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# Organic and functional evaluation of atherosclerosis in renal transplant recipients

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## ORGANIC AND FUNCTIONAL EVALUATION OF ATHEROSCLEROSIS IN RENAL TRANSPLANT RECIPIENTS

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We evaluated atherosclerotic lesions in 18 renal transplant recipients in whom the grafts remained functional after transplantation from living donors at the Sakai Hospital, Kinki University School of Medicine. In each patient, the mean intima-media thickness of the bilateral common carotid arteries (mIMT) was measured by ultrasonography. In the pulse wave test, the ankle brachial index (ABI) and the brachial-ankle pulse wave velocity (ba-PWV) were measured. In 12 (66.7%) of the 18 renal transplant recipients examined, the mean value of ba-PWV was higher than the mean plus 1 standard deviation (SD) in the corresponding Japanese age group. A significant correlation was noted between mIMT (an organic indicator of atherosclerosis) and ba-PWV (a functional indicator of atherosclerosis). The age at the time of test, blood pressure and the pre-transplant duration of hemodialysis had a significant positive correlation with both mIMT and ba-PWV. Thus in renal transplant recipients, organic evaluation of atherosclerosis correlated significantly with its functional evaluation. Both evaluations were proven to be reliable. Many of the renal transplant recipients had complications from atherosclerosis, and several factors seemed to be involved in the onset of atherosclerosis in these patients. Among others, the duration of hemodialysis before transplant correlated particularly closely with post-transplant onset of atherosclerosis, and it seems likely that persistent uremia can stimulate the progression of atherosclerosis.

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**Key words**: Renal transplant recipient, Atherosclerosis, Intima-media thickness (IMT), Common carotid arteries, Pulse wave velocity (PWV)

### INTRODUCTION

Cardiovascular diseases are responsible for a high percentage of all deaths among the Japanese. In most cases of fatal cardiovascular disease, terminal-stage atherosclerosis is present. Atherosclerosis is one of the most important factors determining both graft survival and patient survival<sup>1)</sup>. Functional or organic evaluation of atherosclerosis using noninvasive methods has recently been attempted, and its results have been reported from various specialties<sup>2,3)</sup>. Aortic pulse wave velocity (PWV) measurement is often used for functional evaluation of arterial stiffness. Its application to renal transplant recipients has also been reported<sup>4–6)</sup>. Evaluation of the carotid artery by high-resolution B-mode ultrasound scan has been shown to provide a valid means of functional evaluation of atherosclerosis, and several reports of its application to renal transplant recipients have been published<sup>7–10)</sup>. We recently conducted functional and organic evaluation of atherosclerotic lesions in renal transplant recipients and evaluated the significance of these measurements.

### SUBJECTS AND METHODS

#### Subjects

During the period from July 1999 to June 2003, 19 patients underwent renal transplantation from living donors at the Sakai Hospital, Kinki University School of

Medicine. One of these patients died of cryptococcal meningitis two years after transplantation, but the remaining 18 patients are alive with functioning grafts. These 18 patients were enrolled in this study after they gave informed consent. There were 11 males and 7 females, with a mean age of 42.0 years at the time of testing. Each patient was receiving an immunosuppressive therapy, involving a combination of ciclosporin or tacrolimus with other drugs. The test was conducted when renal graft function was stable (3 months or more after transplantation).

#### Pulse wave test

The pulse wave test was carried out using a FORM PWV/ABI (Colin Corporation). The test was started after the patient remained still in the supine position for 5 minutes. Measurement of blood pressure at bilateral brachial arteries was followed by measurement of the ankle brachial index (ABI) and the brachial-ankle PWV (ba-PWV). The ba-PWV was analyzed on the basis of the mean of right and left ba-PWV.

#### Carotid artery ultrasonography

Carotid artery ultrasonography was performed using a SONOS 4500 (Philips) in combination with a 3–11 MHz linear probe. Each patient received this test in the supine position, with the jaw protruded anteriorly and the head inclined in the opposite direction to allow an extensive area of the neck to be tested. The target site was the common carotid artery. Maximum intima-

media thickness (IMT) and the IMT at two other points (1 cm distant from the maximum point in two directions) were measured. The thickness at these three points was averaged to yield the mean IMT (mIMT). The mIMT on the right side and that on the left side were averaged for analysis. All examinations were carried out by the same experimental technician who was unaware of patient history or laboratory findings.

#### Statistical analysis

Logistic regression analysis was employed for statistical analysis. The coefficient of regression was calculated by the Mann-Whitney test.

### RESULTS

For the 18 patients studied, mIMT ranged from 0.45 to 0.9 mm (mean: 0.60 mm). ABI averaged 1.16 on the right side and 1.15 on the left side. No patient showed marked laterality (difference between right and left sides) in ABI. The lowest level of ABI was 0.97. There was no patient in whom ABI was abnormally low suggesting arterial obstruction. ba-PWV ranged from 1,184 to 2,071 cm/s (mean: 1,477 cm/s). In 12 (66.7%) of 18 patients, the mean value of ba-PWV was higher than the mean plus 1 standard deviation (SD) in

the corresponding Japanese age group (criterion for each age group of the Japanese proposed by Yamashina et al.<sup>11)</sup>, with sex-related differences taken into account).

The mIMT (an organic indicator of atherosclerosis) correlated significantly with ba-PWV (a functional indicator of atherosclerosis) is shown in Fig. 1. There was no sex-related difference in mIMT or ba-PWV. The age at the time of the test had a significant positive correlation with mIMT and ba-PWV (Fig. 2). Body mass index (BMI) ranged from 16.8 to 25.3 (mean: 20.57). There was no significant correlation between BMI and mIMT or ba-PWV. MBP, intermediate between systolic and diastolic blood pressure, ranged from 84.5 to 126 mmHg (mean: 104.1 mmHg). MBP had a significant positive correlation with mIMT and ba-PWV (Fig. 3). Serum creatinine level ranged from 0.6 to 4.8 mg/dl (mean: 1.55 mg/dl). Serum creatinine had no significant correlation with mIMT or ba-PWV. The duration of pre-transplant hemodialysis (preemptive in 2 cases) averaged 56.0 months (maximum: 223 months). The pre-transplant hemodialysis period had a significant positive correlation with mIMT and ba-PWV (Fig. 4). These results suggest that persistence of uremia can stimulate the progression of

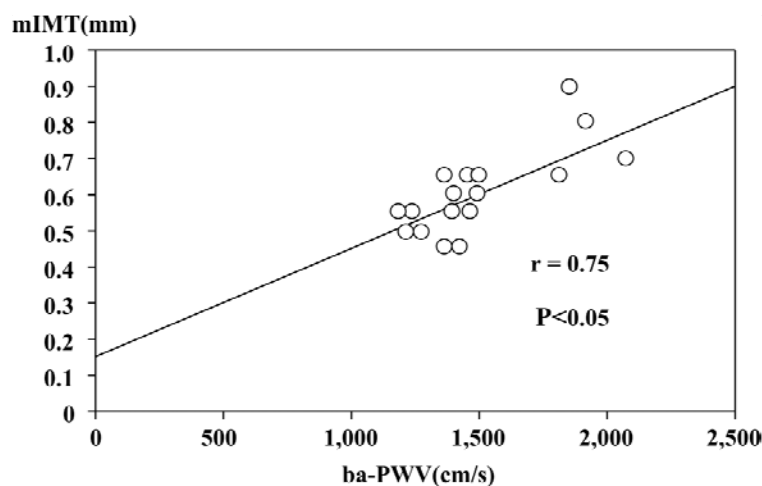


Fig. 1. There was a significant correlation between mIMT and ba-PWV.

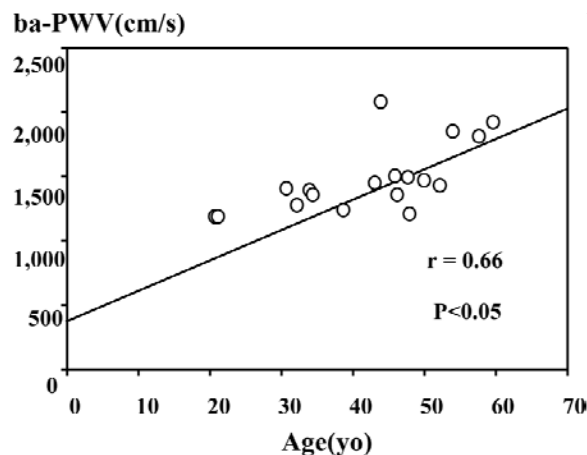
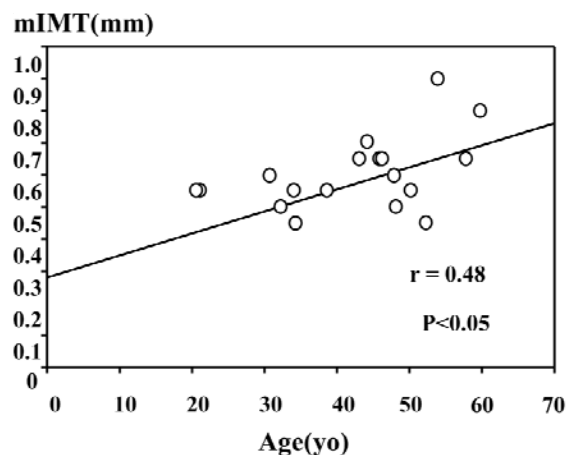


Fig. 2. The age at the time of the test had a significant positive correlation with mIMT and ba-PWV.

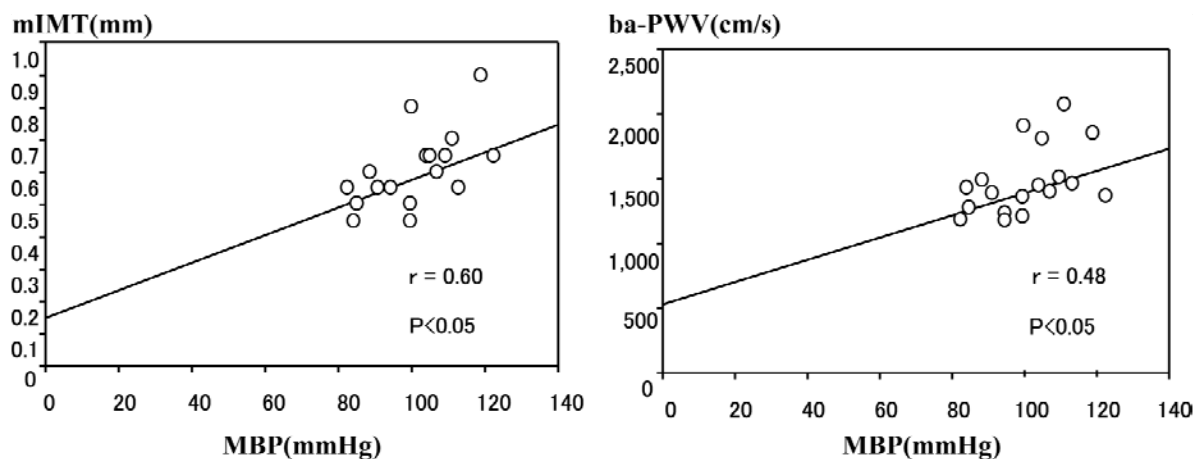


Fig. 3. MBP had a significant positive correlation with mIMT and ba-PWV.

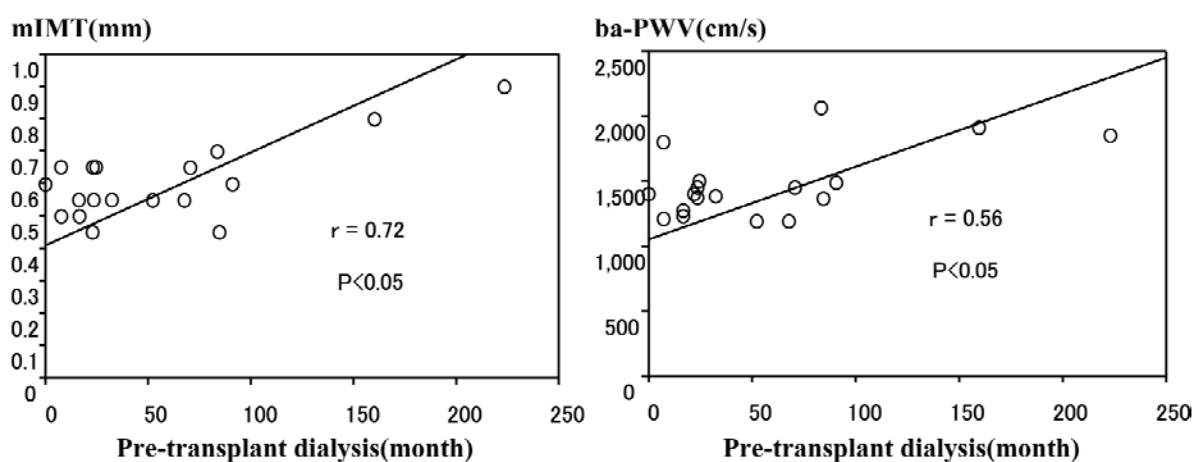


Fig. 4. The pre-transplant hemodialysis period had a significant positive correlation with mIMT and ba-PWV.

atherosclerosis.

### DISCUSSION

From the time ciclosporin began to be used for immunosuppressive therapy after kidney transplantation, the incidence of cardiovascular complications also began to increase. These complications have a significant impact and can determine not only the function of kidney grafts but also the survival of patients<sup>12,13</sup>. Atherosclerosis is the most important risk factor for cardiovascular complications after kidney transplantation. Therefore, to achieve long-term survival of kidney grafts, it is essential that atherosclerotic lesions of kidney recipients are evaluated precisely. Massy et al.<sup>8</sup>) evaluated IMT and plaques for assessment of atherosclerosis in kidney recipients and demonstrated in a prospective study that atherosclerosis is closely related to the onset of cardiovascular complications in kidney recipients. This indicates that evaluation of atherosclerosis is important when predicting the prognosis of patients after kidney transplantation.

Nowadays, simultaneous functional and organic evaluations of atherosclerosis are sometimes carried out. We made these evaluations in the present study and demonstrated a significant correlation between func-

tional and organic evaluation of atherosclerosis. Both methods (functional and organic methods) are reliable, and simultaneous evaluation using both methods seems to allow more accurate evaluation.

As reported by several investigators, atherosclerotic complications are often seen among kidney recipients. Also, in the present study, 67% of all kidney recipients had atherosclerotic complications. Several factors seem to be involved in the onset of atherosclerosis among kidney recipients. One such factor is age. Correlation between age and IMT has been reported by many investigators for patients with uremia and healthy individuals<sup>14,15</sup>. The results of the present study endorse these findings. The mechanism of the progression of atherosclerosis among patients with chronic renal failure has been discussed in detail, and a correlation between atherosclerosis (as evaluated on the basis of IMT) and the duration of hemodialysis has been reported<sup>16</sup>. Also, in the present study, the duration of pre-transplant hemodialysis was the only pre-transplant background variable that correlated with post-transplant atherosclerosis. This suggests that persistent uremia can induce the progression of atherosclerosis, but this mechanism is not explained clearly. Secondary hyperparathyroidism can affect the cushioning function

of larger arteries in patients with end-stage renal failure independently of high blood pressure<sup>17,18)</sup>. This is one reason persistent uremia correlates with progression of atherosclerosis. Definite evidence supporting the correlation between blood pressure and PWV has been reported<sup>19)</sup>. Blood pressure control plays an important role in achieving long-term survival of kidney grafts<sup>20)</sup>. Other factors reported to be associated with atherosclerosis among kidney recipients include cholesterol, hematocrit, fibrinogen, homocysteine and parathyroid hormone<sup>7,18,21,22)</sup>. Atherosclerosis in renal transplant recipients is extremely multifactorial. However, the patient population of this study is quite small. In the future, we need to demonstrate the risk factors of atherosclerosis in renal transplant recipients using multiple regression analysis with large population. Checking these factors involved in atherosclerosis will allow more appropriate management of patients after kidney transplantation.

Some previous studies of the time course after kidney transplantation demonstrated improvement in IMT and PWV after transplantation<sup>5,6,10,18)</sup>. On the basis of such results, IMT and PWV have been recommended as means of follow-up after kidney transplantation. These tests may also be used for evaluation of responses to treatment of atherosclerosis.

The noninvasive methods for evaluation of atherosclerosis used in the present study appear to be useful in the management of patients after kidney transplantation.

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## 和文抄録

## 移植患者に対する器質的および機能的な動脈硬化性病変の評価

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背景：動脈硬化は移植腎生着や患者生存に関わる重要な因子である。そこでわれわれは、腎移植患者に対する動脈硬化性病変の評価を行い、その意義を検討した。

方法：近畿大学医学部堺病院で生体腎移植を施行し生着中である18名の腎移植患者を対象とした。頸動脈エコーでは、左右の平均総頸動脈内中膜複合体厚 (mIMT) を計測した。脈波測定検査は足首上腕血圧比 (ABI) および上腕足首脈波伝導速度 (ba-PWV) を測定した。

結果：測定を行った腎移植患者では18例中12例 (66.7%) で年代別基準値の1SDを超える高値を呈していた。動脈硬化の器質的評価である mIMT と機

能的評価である ba-PWV の両者間に有意な相関を認めた。mIMT と ba-PWV の両者と有意な正相関を認めたのは、検査時の年齢、血圧、移植前の透析期間であった。

結論：腎移植患者における動脈硬化の器質的評価と機能的評価には有意な相関があり、いずれも信頼性のある方法と考えられた。また、腎移植患者は動脈硬化症を合併する例が多く、その発症にはいくつかの因子が関与すると考えられた。なかでも移植前の透析期間は動脈硬化と強く関連しており、尿毒症状態の長期化が動脈硬化の進行を誘発すると考えられた。

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